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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/908,453	08/07/97	RUVKUN	G 08472/704002

HM12/0607

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EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	24

DATE MAILED: 06/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	08/908,453	RUVKUN ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10-13,15,16,18-20,29 and 30* is/are pending in the application.

4a) Of the above claim(s) *1-4,14 and 21-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10-13,15,16,18-20,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on 4-6-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/908,453 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 9 and 17 have been canceled.

3. Amendments to claims 8, 10-12, 15, 16, 29, and 30 have been entered.

4. Claims 1-4, 14, and 21-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 15.

5. Claims 8, 10-13, 15, 16, 18-20, 29, and 30 are instantly under consideration in the instant application.

Claim Rejections - 35 U.S.C. ' 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. In view of the amendment to claims 8, 10, 11, and 29-30, the written description rejection has been withdrawn.

8. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 18-20 are rejected being dependent on rejected claim 15.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

Claimed invention is drawn to a method of identifying compounds that modulate the expression of AGE-1 gene. When the claims are analyzed in light of the specification, instant invention encompasses AGE-1 gene that would comprise the promoter region of the AGE-1 gene driving the expression of AGE-1 coding sequences. However, the specification discloses only SEQ ID No 1 which is the amino acid sequence of AGE-1 polypeptide and SEQ ID NO 2 which is the cDNA sequence encoding the amino acid sequence of SEQ ID NO 1. It is noted that the specification does not disclose the promoter region of the AGE-1 gene and the disclosure of which will be essential for the claimed invention. It is noted that the claimed invention of claim 15 uses the AGE-1 DNA of claim 8 which is a cDNA and therefore a cell expressing the AGE-1 of claim 8 wherein the expression of AGE-1 is under any other promoter would not be indicative of the gene expression of AGE-1. The specification does not provide any other relevant identifying characteristics, nucleotide sequence, specific features and functional attributes that would distinguish AGE-1 promoter from any other promoter.

The limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the complete AGE-1 gene sequences including the promoter except for the cDNA of SEQ ID NO 2, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed invention.

9. Claims 8, 10-13, and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons set forth in the previous office action of 8-17-99, 5-4-00, discussions therein and as discussed below.

It is noted that amendment to claim 8 has narrowed the scope to nucleic acids encoding a protein that has 95% amino acid sequence identity. Furthermore, after amendment claim 29 is dependent on claim 8. However, these amendments have not addressed the enablement issues raised in previous office actions. As stated in the previous office actions of 8-17-99 and 5-4-00, the specification is not enabling for the claimed invention because the specification does not provide sufficient guidance as to how an artisan would have made all the claimed polynucleotide sequences, vectors, and host cells expressing all the claimed polynucleotide sequences and would have used those without undue experimentation.

As reiterated in the previous office actions, the major issue is: just because the claimed polypeptides have amino acid identity to a known protein, does not ensure that the polypeptide or its derived or cloned fragments would have the same function or even any function as that of the protein. Only because a protein comprises a domain that has 37% sequence similarity with a given functional domain in another protein, will it have the activity of the said domain and as noted earlier, there is no evidence in the specification to demonstrate that the claimed polypeptides would have a kinase activity. Neither the specification nor the prior art on record, at the time of the filing of the application, provides any guidance whether AGE-1 polypeptide has PI3-kinase activity. The only support for such activity is the observation that the polypeptide when compared with known proteins of the database has similarity to kinase domain. There is nothing on the record to show whether art recognized assay conditions would be sufficient to support kinase activity of AGE-1 polypeptide in vitro because no working examples of any such assay have been disclosed in the specification or in the prior art on record. There is no evidence of record to indicate the amino acid sequence of SEQ ID NO 2 has been purified or has been recombinantly expressed in an isolated cell. In the absence of any functional assay for the polypeptide encoded by the claimed polynucleotide, how would an artisan have known how to use the claimed polynucleotides, expression vectors comprising these polynucleotide segments, host cells comprising these polynucleotide expression vectors, and producing the polypeptides encoded

by these polynucleotides or preparing membranes of host cells expressing these polynucleotides. Regarding the limitation of polynucleotides that have at least 95% sequence identity, it is reiterated that if it is debatable whether SEQ ID NO 1 protein has a certain activity, how would the variants or mutants of the protein have the activity. Regarding claims 29 and 30 it is noted that it is not clear from the specification as to what is the role of the listed amino acids and whether making a change in any of these amino acids would alter the activity of the polypeptide and if so, what would be the effect. The listed 50+ amino acids are scattered all over the protein and consequence of changing any of the 50% of these amino acids is not clear from the teachings of the specification. For example if the first 25 listed amino acids are changed what would be the activity of the protein, compared to when the last 25 amino acids are changed. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6).

In view of the lack of the assay for the protein of SEQ ID NO 1, how would an artisan know the activity of the proteins with different combinations of changes in the amino acids? In summary, an artisan would be required to carry out extensive experimentation to devise methods to assay the activity of the protein encoded by the claimed polynucleotides. Therefore, in view of the breadth of the claims and the lack of in the specification as well as in the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use claimed invention.

Response to Applicant's Arguments:

Applicants have argued the rejection of claims 8, 10-13 and 15, 16, 18-20 together. Accordingly, these arguments would be addressed together in the next paragraph.

10. Claims 15, 16 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons set forth in the previous office action of 8-17-99 and 5-4-00 and discussions therein and as discussed below.

Amendment to claims 15 and 16 has included a step of measuring the AGE-1 gene expression or PI 3-kinase activity in the cell. As disclosed in the previous office actions, and above in the paragraph on enablement of claims 8, 10-13, the specification as filed is not enabling for the claimed invention because the specification does not provide any evidence as to (i) what is the activity of the AGE-1 polypeptide; (ii) if the activity of AGE-1 polypeptide is not known, how would an artisan have assayed the AGE-1 activity in vitro; (iii) whether the polypeptides, that would have had 95% identity with the polypeptide disclosed in SEQ ID No 1, would have the activity of AGE-1 polypeptide; (iv) whether the AGE-1 polypeptide from animals would have had the same activity as the AGE-1 polypeptide disclosed in SEQ ID No 1; (v) whether an artisan would have been able to carry out the claimed method in any animal or nematodes? The specification does not provide any guidance as to how an artisan would have dealt with these problems and therefore, an artisan would not have been able to make and use the invention as claimed without undue experimentation. Regarding claim 15 it is further noted that the method recites expression of AGE-1 gene and its modulation by compound, which could be interpreted that the compounds would modulate transcription of the AGE-1 gene, however, the specification does not teach the sequence structure of the promoter region of AGE-1, therefore, it is not clear as to how this method can be carried out in vitro or in vivo with the guidance provided in the specification.

Resp nse t Applicant's Arguments:

Applicant's arguments have been fully considered, however, they are not deemed persuasive because, these arguments do not persuasively respond to the points raised in the previous office action.

Applicants have first argued that changing the scope of the claimed invention to 95% sequence identity has addressed the rejection, however, these arguments are not persuasive because the primary issue is the activity of the protein of SEQ ID NO 1 and the specification is not enabling for that. If so, how can it be enabling for the 95% identical sequences?

Next, Applicants have argued that even though AGE-1 represents a divergent class of PI 3-kinase, there is no reason to believe that the polypeptide of the claimed invention would not have the PI 3-kinase activity. In support Applicants argue that the probability of random alignment is very low and therefore the low sequence identity between AGE-1 and mammalian PI 3-kinase is of little importance. Applicants cite a paper published by Morris et al and argue that this paper describes that AGE-1 is believed to encode a PI3-kinase and that because these results were peer reviewed by some top scientists in the area of research, there can be no question that AGE-1 nucleic acids encode PI 3-kinase. In response, it is noted that the statement that Applicants are referring indicates only a possibility that AGE-1 could be a PI 3-kinase, it does not say that it is PI 3-kinase. Applicants have also cited an article by Babar et al, which states that PI 3-kinase inhibition mimics the effects of AGE-1 mutation. In response to these arguments it is noted that the results of Morris et al and Babar et al are circumstantial and the probability of random alignment is a theoretical result. It is interesting that even 5 years after the publication of the Morris paper, which teaches the amino acid sequence of AGE-1, there is no publication or evidence of record regarding the activity of the purified protein or recombinantly expressed protein. This clearly indicates difficulties in assaying the activity of the protein and expression of the protein in vitro. Therefore, the issue raised in the enablement rejection is a valid issue and Applicants' arguments have not been able to provide substantial evidence

that AGE-1 encodes a PI 3-kinase and how would activity of AGE-1 be assayed in vitro or in vivo?

Applicants have next argued that three subunits of mammalian PI 3-kinase may be subsumed by a singly AGE-1 PI 3-kinase in nematodes, however this is a significant statement that one protein has functions of three proteins, but there are no indications as to what part of the AGE-1 protein would correspond to which of the three mammalian kinases. If the protein in the nematodes has three roles to play, how can an assay for three different proteins be adopted to assay the function of a protein, which has the activity of all the three proteins? It is reiterated that even after 5 years after the effective filing date of the application, there is no evidence of record that a purified AGE-1 protein or recombinant AGE-1 protein has been prepared or reported in the literature, which indicates that an artisan would have to devise an assay system for the claimed methods and in the absence of sufficient guidance in the specification, such experimentation would be considered undue.

In conclusion, the specification as filed fails to provide sufficient guidance, working examples and evidence as to how an artisan of skill would have practiced the claimed invention without undue experimentation.

Claim Rejections - 35 U.S.C. ' 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 12, 15, 16, 18-20 and 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is indefinite because it is unclear as to what is meant by the phrase "encoding an AGE-1 polypeptide positioned for expression in the cell"?

Claim 15 is indefinite because it is unclear as to what is meant by the phrase "measuring AGE-1 gene expression in said cell, a decrease in AGE-1 gene expression in said cell following contact with said candidate compound, related to an untreated cell"?

Claim 16 is indefinite because it is unclear as to what is meant by the phrase "measuring the PI 3-kinase activity of said cell, a decrease in AGE-1 PI 3-kinase activity of said cell following contact with the candidate compound, related to an untreated cell"?

Claim 29 is indefinite because it is unclear whether the recitation of the limitation "50%" is in reference to number of amino acids at a particular residue or in reference to the total number of residues recited.

13. Claims 8-13, 15-20, and 29-30 are free of prior art of record because they are drawn to a nucleic acid of AGE-1 protein, a host cell expressing the claimed nucleotides and assay methods for identifying compounds that modulate AGE-1 polypeptides.

14. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or

proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER